*REMARKS/ARGUMENTS*

*Claim Amendments*

Claims 40, 61, and 64 have been amended to make it clearer that the claimed method is indeed an *in vitro* method as supported by specification page 16, line 6. Claims 16, 31, 59, 60, 62, and 63 have been amended to clarify that the alkylating agent causes cytotoxic lesions at the $O^6$-position of DNA guanine residues, as supported by the specification at page 1, lines 1-6 of paragraph [0002]. No new matter has been added. The present application is under non-final rejection; see Examiner Interviews below. Accordingly, the claim amendments should be entered.

*Office Action*

Claims 1-15 and 49-58 are indicated allowable. Claims 16, 17, 31, 32, 40, 41 and 59-64 have been rejoined. However, claims 16, 17, 31, 32, 40, 41, and 59-64 are rejected under 35 USC 112, first paragraph, for an alleged non-enablement and claims 16, 17, 59, and 62 are rejected under 35 USC 112, second paragraph, for an alleged indefiniteness.

*Examiner Interviews*

Applicants wish to thank Examiner Cecilia Jaisle for the courtesies extended to Xavier Pillai, one of Applicants' attorneys, during the telephonic interviews held on October 24, 2008 and November 5, 2008. During the interviews, the Examiner agreed to withdraw the finality of the outstanding Office Action, as Applicants have not been provided an opportunity earlier to address at least one of the § 112 rejections. Applicants are grateful for withdrawing the finality of rejection. The Examiner also clarified the indefiniteness rejection and indicated that if the claims were amended to indicate that "guanine" is that of the DNA, the rejection would be withdrawn. Applicants gratefully acknowledge the Examiner's suggestion.

*Discussion of Rejections*

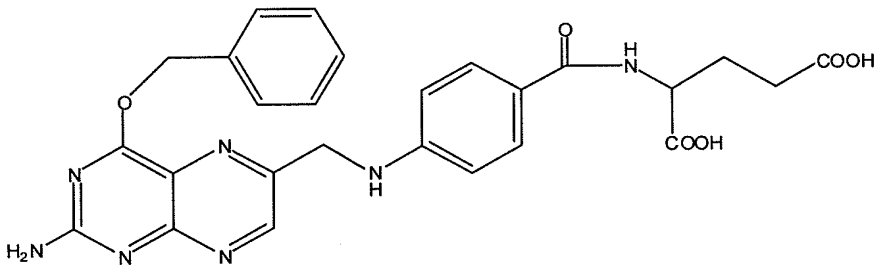
*1. Non-enablement Rejection*

Claims 16, 17, 31, 32, 40, 41, and 59-64 are rejected under 35 USC 112, first paragraph, for an alleged non-enablement. The Office Action states that the specification is

enabling for inactivation of human $O^6$-alkylguanine-DNA alkyltransferase ("AGT") *in vitro* but it does not, according to the Office Action, reasonably provide enablement for (a) a method of enhancing chemotherapeutic treatment of tumor cells in a mammal with an antineoplastic alkylating agent that causes cytotoxic lesions at the $O^6$-position of guanine comprising co-administering a compound or salt of claims 1, 5, or 9 and an antineoplastic alkylating agent which causes cytotoxic lesions at the $O^6$-position of guanine (claims 16, 17, 59, and 62); (b) a method for treating tumor cells in a mammal by administering a compound or salt of claim 1 (claims 31, 32, 60, and 63); and (c) a method of inhibiting the reaction of $O^6$-alkylguanine-DNA alkyltransferase with an alkylated DNA by reacting the $O^6$-alkylguanine-DNA alkyltransferase with a compound or salt of claim 1 (claims 40, 41, 61, and 64).

Applicants have amended claims 40, 61, and 64 to expressly recite that the reaction is carried out *in vitro*. Claim 41 is dependent upon claim 40. Accordingly, the non-enablement rejection of these claims has been rendered moot. Therefore, the rejection, as applied to claims 40, 41, 61, and 64, should be withdrawn.

In regards to the rejection of claims 16, 17, 31, 32, 59, 60, 62, and 63, applicants submit a Rule 132 Declaration from Anthony E. Pegg, Ph.D., which through, *in vivo* data, shows that a compound of the claimed invention, $O^4$-benzylfolate (see formula below), inhibits AGT in tumor-induced mice; see paragraphs 3-5.




Applicants submit that the foregoing is a strong evidence that the presently claimed invention is enabled as required under the statute.

The Office Action contends, at page 8, point 4, that "the art indicates the need for undue experimentation." In support of this contention, the Office Action states that Ishiguro et al., *Mol. Cancer Ther.* 2005, *4*, 1755-1763, studied the role of $O^6$-alkylguanine-DNA

alkyltransferase in the cytotoxic activity of cloretazine and reported "the need for further research." The Office Action refers to the following excerpt from Ishiguro et al.:

> DNA cross-linking agents occupy a key position in the currently available cancer chemotherapeutic arsenal. Although the precise mechanisms by which these agents preferentially kill tumor cells remain unclear, it is generally accepted that rapidly dividing cells are more susceptible to such assault, whereas normal cells possess the capacity to recover from DNA damage by genome surveillance mechanisms. Compounds that chloroethylate the $O^6$ position of guanine are unique for the following reasons. First, studies conducted with chloroethylnitrosoureas and 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)hydrazine (90CE) have provided evidence that $O^6$-choloroethylguanine is the critical DNA lesion that progresses to lethal interstrand DNA cross-links. Secondly, the $O^6$-alkylguanine lesion is subject to repair by $O^6$-alkylguanine-DNA alkyltransferase. Finally, variability in the AGT content exists between tumor and host cells. Thus, a difference in AGT content in tumor and host cells constitutes an exploitable target resulting in a therapeutic basis for the antineoplastic efficacy of cloretazine.

Applicants submit that the above excerpt does not support the contention of the Office Action. On the contrary, the above excerpt shows that the presently claimed invention is on a strong scientific footing. The presently claimed invention enhances the efficacy of alkylating (chloroethylating) agents that alkylate the $O^6$-position of the DNA of tumor cells. Such chlorethylated DNA proceeds to form interstrand G-C DNA crosslinks, leading to the tumor cell death. AGT, as a DNA repair protein, attempts to dealkylate the chloroethylated DNA. The compounds of the invention deactivate the AGT so that the chloroethylation and interstrand crosslinking can proceed unhindered.

Ishiguro et al. clearly states that "DNA crosslinking agents occupy a key position in the currently available cancer chemotherapeutic arsenal." Ishiguro et al. goes on to state that "compounds that chloroethylate the $O^6$-position of guanine are unique." Ishiguro et al. confirms that "studies conducted with chloroethylnitrosoureas and 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)hydrazine have provided evidence that $O^6$-chloroethylguanine is the critical DNA lesion that progresses to lethal interstrand DNA crosslinks." Ishiguro et al. also confirms that "$O^6$-alkylguanine lesion is subject to repair by $O^6$-alkylguanine-DNA alkyltransferase." Ishiguro et al. also confirms that "there is variability in the AGT content in tumor and host cells" and that this variability "constitutes an exploitable target resulting in a therapeutic basis for the antineoplastic efficacy of cloretazine."

The foregoing clearly supports the presently claimed invention, and in no way supports the Office Action's contention that there is a need for undue experimentation or further research.

In view of all of the foregoing, the non-enablement rejection should be removed.

*2. Indefiniteness Rejection*

Claims 16, 17, 59, and 62 are rejected under 35 USC 112, second paragraph, for an alleged indefiniteness. The Office Action states that "it is not understood how an antineoplastic alkylating agent can cause cytotoxic lesions at the $O^6$-position of guanine." The Office Action is asking: "How can lesions be caused on a molecule?"

Applicants have amended the claims, as discussed, to indicate that "guanine" refers to the DNA guanine residue. Accordingly, the indefiniteness rejection should be removed.

*Conclusion*

A favorable decision is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

Xavier Pillai, Ph.D., Reg. No. 39,799
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

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